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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,683	10/02/2003	David Borcherding	USA3960 US CNT	8394

5487 7590 08/10/2006

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/677,683	**Applicant(s)** BORCHERDING ET AL.	
	Examiner Mark L. Berch	**Art Unit** 1624	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See memo*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-19,21-35 and 45-49*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See memo.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Mark L. Berch
Primary Examiner
Art Unit: 1624

DETAILED ACTION

The amendment filed 07/28/2006 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because: The proposed amendment raises new issues that would require further consideration and/or search.

The amendments to claim 5 are problematic. The "follicular reticulum"(sometimes called FDC-reticulum) is a sponge-like network of intertwining of FDC dendrites. It is not a name of a neoplasm. Hodgkins disease is an ordinary Lymphoma; it is not a mixed neoplasm, as was stated previously in point 11. The term "cell sarcoma" is just a piece of a name. There is for example Clear cell sarcoma of the kidney (CCSK), Synovial cell sarcoma, Spindle Cell Sarcoma, reticulum cell sarcoma, Malignant Granular Cell Sarcoma and others. These are not mixed neoplasms, and it is not clear what disorder(s) are intended. "Lymphoid tissue type" is also part of a name.

The traverse remains unpersuasive. The same numbering is used

1. Applicants continue to refuse to answer, saying instead, "The office applies an "always standard" relating to what constitutes a CDK." The examiner is not applying any standard at all. The examiner is pointing out that what constitutes a CDK is not clear, and hence the scope of claims is not clear. There are things called "CDK like" kinases which do not have a numeral after CDK, but instead have e.g. the letter L. Applicants are still not saying whether these are included or not. There is no agreement on whether ICK should be considered a CDK or a MAP kinase. These and other examples of things which may or may not be CDK are presented as evidence that the scope of what is CDK is not clear. Simply

having multiple names per se is not a problem. The problem is that the scope of the term is unclear, as evidence by applicants' inability to answer these specific questions.

2,3. The amendment, if entered, would have addressed the issue.

4. The "substituted by a N atom" text appears in the third line below the claim 1 structures for the aromatic rings. It is impossible for these rings (or any rings) be substituted by a nitrogen atom, because an nitrogen requires three H atoms to replace, and these rings have only one. In the response, applicants continue to insist that "substituted by" "has the meaning that one replaces the other." But the actual verb here is "substituted", not "replaced". Applicants give the analogy of a substitute teacher. "Substituted" is a chemical term. It means that the H on an atom is replaced, not the atom itself. That is the standard use of substituted. Otherwise, the verb is replaced, as in "The term "heteroaromatic" refers to an aromatic ring of C.sub.5-C.sub.10 carbon atoms, where one or more carbon atoms is replaced with a nitrogen, oxygen or sulfur." (from the specification).

5, 6. The amendment, if entered, would have addressed the issue.

7. Applicants point to page 4, lines 5-7, but that 3-7 is not required by the claim, and limitations mentioned in the specification are not read into the clims (unless it is a matter of defining a specific term). Further, this shed no light whatsoever on the question on what the nature of the other atoms are, whether the ring can be bridged, etc.

8-12. The amendment to, if entered, would have addressed the issues.

The traverse on the enablement rejection is unpersuasive.

A. Inoperative embodiments. While some incidental inclusion of possible inoperative embodiments is not a problem, when operativeness has been properly challenged, it is

incumbent on applicant to limit the claims accordingly, cf. *In re Harwood*, 156 USPQ 673, *In re Cook*, 169 USPQ 298, I*n re Langer*, 183 USPQ 288, *In re Corkill*, 226 USPQ 1005, 1009, and *In re Rainier*, 153 USPQ 802. MPEP 2164.08 states, "The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

B. Scope of compounds. This is simply one of several factors. Ra provides for a vast range of compounds, because substitution is so highly nested and there are so many different choices. The variable is important because, as the remarks appear to state, without it the compounds are not effective for the intended purpose. Hence, this is a factor in the direction of undue experimentation.

C. Range of disorders. The purpose of the listing here is to establish the collosal range that is actually covered. The listing establishes the great diversity of the disorders, and hence is a factor in the direction of undue experimentation. The extraordinary range of disorders is also evidence by the fact that the specification devotes pages 7-16 to such a listing, which is by no means exhaustive.

D. Apoptosis in claims 15-20. Applicants state, "There is no requirement in the claim language that the blocking has to be complete blocking in all cells as apparently inferred from the office action." This is not agreed with. Claim 15 says, "preventing apoptosis in cells". This is embracive of ANY type of apoptosis in ANY type of cell. No qualifiers appear, and the PTO will not read into the claims any limitation from the specification. As is indicated in the quotation from *Wright* in A. above, the full scope of the claim must be enabled. Applicants are reminded that there is no "master switch" for apoptosis. As was

set forth previously, there are 3 independent mechanisms by which a cell commits suicide by apoptosis. The point here is that of course undue experimentation is involved, because this is an extremely complex and little understood process. Moreover, the examiner must point out that the compounds are alleged to be effective against cancer and for preventing apoptosis. These are contradictory utilities. Inducing apoptosis is one of the body's main anticancer mechanisms. Important anti-cancer drugs such as paclitaxel and tamoxifen operate by inducing apoptosis. Indeed, it is becoming increasingly clear that the most important determinant of tumor resistance may be a generalized resistance to induction of apoptosis. That is, tumor cells manage to survive because they are resistant to the body's apoptosis mechanisms. Drugs that suppress apoptosis would be expected make cancer worse. The same is true for some important autoimmune disorders, notably MS and lupus and Sjögren's syndrome, all of which involve having too little apoptosis. Certain autoimmune diseases appear to arise when self-reactive lymphocytes don't die when they are supposed to die.

As for "complete blocking", this is a non-issue. Apoptosis is either blocked or is not blocked.

E. Direction and guidance. Applicants here argue, "Further, the citation of experimentation of drugs that foundered is evidence that such experimentation is in fact routine, not undue." This is illogical. As the examiner pointed out, many promising anti-cancer drugs have foundered because those of one skilled in the art were unable to find a dosage that actually works. This indicates that it is not a matter of routine experimentation to go from promising in vitro (or animal) experiments to human success.

The dosage in the specification, which is the same regardless of whether one is speaking of asthma or cancer, is thus of no real value because it is completely generic.

F. State of the prior art. The fact that there are no other piperidine-amino-purines in use as e.g. anti-cancer agents means that one cannot piggy-back on what is known with structurally similar compounds. As a result, more work needs to be done than would be in a situation where there were such compounds in use.

G. Lack of working examples. This is a legitimate factor in a *Wands* analysis. Applicants are claiming e.g. prevention of apoptosis or the treatment of Type I diabetes without any evidence that these compounds can actually do such a thing. An enablement rejection can be sound when the specification's "statements reflect no actual observations. Moreover, we have not been shown that one of ordinary skill would necessarily conclude from the information expressly disclosed by the written description that the active ingredient" does what the specification surmises that it does. *In re Cortright*, 49 USPQ2d 1464. That appears entirely applicable here. There are no actual observiations that would lead to a conclusion that these compounds are effective for e.g. prevention of apoptosis or the treatment of Type I diabetes. Applicants have cited *Atlas Powder* which does say, "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid...if the number of inoperative combinations becomes significant, and in effect, forces one of ordinary skill in the art to experiment unduly...the claims might indeed be invalid" This can arise in a situation where the elements may be effective, but some of the specific permutations, the specific combinations, might not work. The examiner is not concerned with incidental circumstances where the compounds might not work. But applicants are claimed that their compounds are active against CDKs generally, even

though the experience with CDK inhibitors, even the more non-selective inhibitors, is that they don't act generally. Moreover, the examiner must note that this decision from 1984 has been perhaps superceded to some degree by the more demanding standards of *Wands* and *Cortright* and *Wright*.

H. Skill in the art. When the examiner wrote "The cancer therapy are remains highly unpredictable", applicants reply that "This goes to the issue of anticipation and obviousness". That is not the issue. The more unpredictable a technology is, the more experimentation is involved. As was stated in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) "the scope of enablement varies inversely with the degree of unpredictability of the factors involved."

I. Autoimmune disease. These diseases are, historically, among the most difficult to treat, and indeed, even to diagnose. Applicants argue that "all require proliferation of cells to effect the disease state." But "proliferation of cells" of cells is an extremely general term. Its not just autoimmune disease that involves "proliferation of cells". Most human disease involves proliferation of cells. All infectious disorders, all inflammatory disorders, nearly all skin and bone disorders, and nearly all neonatal disorders, for example, involve proliferation of cells. If applicants' reasoning were accepted, the fact that their compounds inhibit a handful of CDK complexes would support treatments of the majority of human disease, which is absurd. In terms of B-cells, the examiner wrote previously, "In another place, applicants state that "Preventing or minimizing activation and proliferation of B cells...", but applicants have not shown that their compounds do, in fact, prevent the activation, etc of B-cells. In fact, the examiner cannot even locate, in this 183 page specification, even any mention of applicants compounds having any effect at all on B-cells."

Applicants now reply that there is no nexus between enablement and B-cells. Actually, it was applicants who raised the B-cell argument. The remarks of 2/16/2006 stated, "Preventing or minimizing activation and proliferation of B-cells responsible for the autoimmune antibodies would be expected to ameliorate symptoms of associated autoimmune diseases." In rebuttal to that, the examiner replied, in effect that applicants have not shown that their compounds were capable of preventing or minimizing activation and proliferation of B-cells. Moreover, to the extent that activation and proliferation of B-cells is quite important in the immune system, this failure provides reason to doubt that these compounds can indeed treat autoimmune disorders generally.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Berch

Primary Examiner

Art Unit 1624

8/4/2006